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Review

Effectiveness of personal protective measures in reducing pandemic influenza transmission: A systematic review and meta-analysis

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ABSTRACT

The goal of this review was to examine the effectiveness of personal protective measures in preventing pandemic influenza transmission in human populations.

We collected primary studies from Medline, Embase, PubMed, Cochrane Library, CINAHL and grey literature. Where appropriate, random effects meta-analyses were conducted using inverse variance statistical calculations.

Meta-analyses suggest that regular hand hygiene provided a significant protective effect (OR = 0.62; 95% CI 0.52–0.73; $I^2 = 0\%$), and facemask use provided a non-significant protective effect (OR = 0.53; 95% CI 0.16–1.71; $I^2 = 48\%$) against 2009 pandemic influenza infection. These interventions may therefore be effective at limiting transmission during future pandemics.

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Contents

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1. Introduction

Influenza pandemics may arise from antigenic shifts, when reassortment between different viral strains results in the emergence of a novel influenza virus to which most individuals are immunologically naïve (Zambon, 1999). If this new pathogen causes clinical illness in humans and is able to transmit effectively between humans, a global pandemic may occur. This has happened four times in the past one hundred years: the 1918 Spanish flu, the 1957 Asian flu, the 1968 Hong Kong flu and the 2009 Swine flu. Together these events have resulted in millions of cases of illness, hospitalization and death, as well as a significant social and economic burden (Humphries, 2013; Henderson et al., 2009; Guan et al., 2010; Simonsen et al., 2013). The Spanish flu demonstrates the catastrophic potential of such events, having caused between 20 and 50 million deaths globally (Humphries, 2013; Jordan, 1927; Patterson and Pyle, 1991; Johnson and Mueller, 2002). Advances in medicine and public health render such dramatic consequences unlikely today (Saunders-Hastings and Krewski, 2016). The emergence of antivirals, vaccines and mechanical ventilators should help protect from such a catastrophic pandemic in the future, and pandemic-attributable mortality has decreased in the three influenza pandemics since the Spanish flu[9]. However, the unpredictable nature of influenza pandemics, coupled with increasing opportunities for viral reassortment, necessitate further studies of appropriate mechanisms to respond to such events and mitigate their impact.

The irregular cycle of influenza pandemics makes them difficult to study, with most of the available, scientifically rigorous data deriving from the recent 2009 pandemic. This is problematic given that the 2009 pandemic strain — A(H1N1)pdm09 — is known to have been quite mild, with hospitalization and death rates similar to recent seasonal influenza (Henderson et al., 2009). The disease characteristics of future pandemics may differ substantially from those in the past. Little is known about the effectiveness of a suite of potential interventions to interrupt pandemic influenza infection. This is especially true of non-pharmaceutical measures such as social distancing (school closure, patient quarantine) and personal protective measures (PPMs). Pharmaceutical measures such as pandemic vaccination are effective (Breteler et al., 2013; Demicheli et al., 2014; Manzoli et al., 2009; Yin et al., 2012; Saunders-Hastings et al., 2016), but may not be available in the early stages of a pandemic influenza outbreak (Madhav, 2013; Longini et al., 2004). Social distancing policies, meanwhile, are of uncertain effectiveness, and are often expensive, unpopular and difficult to implement (Isfeld-Kiely and Moghadas, 2014; Perez Velasco et al., 2012; Borse et al., 2011). Consequently, patient quarantine has not been broadly implemented since the 1918 pandemic (Markel et al., 2006), while uncertainty regarding the effectiveness of school closure has limited its implementation over the course of the past three pandemics (Trotter et al., 1959; Earn et al., 2012). However, PPMs such as respiratory etiquette, hand hygiene and the use of facemasks are inexpensive and easy to implement, and are commonly recommended and undertaken during influenza outbreaks (Aledort et al., 2007; Aiello et al., 2010a; van der Weerd et al., 2011).

The primary objective of this review and meta-analysis is to quantify the effectiveness of PPMs in reducing the risk of human-to-human pandemic influenza infection. A secondary objective is to assess the relative effectiveness of these interventions. This is currently an important knowledge gap: a search for existing systematic reviews evaluating pandemic influenza interventions found only a single systematic review (Wong et al., 2014) on the effectiveness of PPMs in preventing pandemic influenza infection; focusing specifically on hand hygiene in the community, the review found only one study that was conducted during an influenza pandemic (Suess et al., 2011). However, the authors only included randomized control trials (RCTs) in their analysis, potentially missing important insights from observational studies. Given the important role PPMs may play in the early stages of a future pandemic, this review provides an important and timely assessment of the state of PPM literature and, where possible, quantification of pooled estimates of PPM effectiveness in interrupting pandemic influenza transmission.

2. Methods

2.1. Overview

Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines were used to guide the development of the systematic review methodology (Appendix A) (Moher et al., 2009). A protocol was developed *a priori* a registered in the National Institute for Health Research International Prospective Register of Systematic Reviews (PROSPERO) (Saunders-Hastings et al., 2016).

2.2. Search strategy

The literature search was conducted by PSH on June 30, 2016, with no language or date restrictions. Searches were conducted across five databases: PubMed (all dates), Medline via Ovid (1946-June 30, 2016), Embase via Ovid (1947-June 30, 2016), Cochrane Library via Ovid (all dates) and the Cumulative Index to Nursing and Allied Health (CINAHL; all dates). Database-specific variations are included in Appendix B. To supplement these searches, researchers conducted searches of the reference lists of included studies, and of the grey literature using Google Scholar.

2.3. Eligibility criteria and study inclusion

In this review, investigators sought to assess the effectiveness of commonly recommended PPMs in reducing the risk of pandemic influenza infection in humans. Personal protective measures included any form of hand hygiene, use of facemasks or respiratory etiquette (covering mouth during coughing and sneezing). Interventions more commonly recommended for healthcare staff, and less likely to be implemented in community settings, were not considered. These interventions include the use of goggles, gowns and gloves to prevent influenza transmission. Table 1 lists the relevant eligibility criteria developed *a priori* and applied throughout the screening process.

All citations were imported into the web-based systematic review software DistillerSR (Evidence Partners Incorporated, Ottawa, Canada). Following deduplication, two independent, blind reviewers conducted title and abstract screening using a pilot-tested DistillerSR screening form that reflected the eligibility criteria. An assenting response from at least one reviewer resulted in article inclusion for full review, where articles were again subjected to blind review by two independent reviewers using a piloted DistillerSR form. At this stage, disagreements were resolved by consensus; third-party arbitration was implemented as necessary.

2.4. Data extraction

Two independent reviewers (PSH, JC) extracted data from included studies using an adapted data collection form developed by The Cochrane Collaboration (Anon., 2013). The form collected information on study population(s), methods, intervention(s), outcome measure(s) and results.

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Table 1
Eligibility criteria for assessed studies.

Category	Inclusion Criteria	Exclusion Criteria
Population	Humans exposed to a pandemic influenza	*In vivo* and *in vitro* laboratory studies, and non-human species
Intervention(s)	Any form of hand hygiene, respiratory etiquette, or the wearing of facemasks	No intervention or other interventions, including vaccination, antiviral use, school or work closure, or contact reduction
Comparison(s)	The impact or effectiveness of an intervention of interest compared to no intervention or other forms of intervention.	No comparisons made
Outcome(s)	Quantified change in risk of pandemic influenza transmission	No quantified impact
Study type	Randomized trials, case-control, cohort, and cross-sectional studies	Predictive mathematical modeling studies; case study and case series reports; case-crossover, crossover, before-after, and ecologic studies; expert opinion and editorials; systematic reviews and meta-analyses

2.5. Quality assessment

Quality assessment was conducted for included studies during the data extraction process. Tables assessing the risk of bias for randomized trials, case-control and cohort studies were included in the data extraction form. Quality assessment of randomized trials adopted the Cochrane Collaboration's tool for assessing risk of bias (Higgins et al., 2011). Quality appraisal for case-control and cohort studies was done using the Newcastle-Ottawa scale (Wells et al., 2014). Both tools have been externally validated and are commonly used in reviews of public health interventions (Higgins et al., 2011; Stang, 2010). Disagreements regarding potential sources of bias were discussed and resolved by consensus. The quality of cross-sectional studies was not assessed, as the risk of bias in these studies was deemed to be innately high, and cross-sectional studies were excluded from data pooling. Study quality was not used as an eligibility criterion; rather, potential sources of bias are noted in the discussion of the implications of review findings.

2.6. Data synthesis and analysis

Data from included studies were grouped based on categories of interventions and outcome measures. Synthesis proceeded in a two-stage process. Comparable data and risk estimates from studies with similar interventions and outcome measures were imported into Revman 5.3.5 (http://tech.cochrane.org/revman). Where possible, we used estimates of effect from models adjusted for the maximum number of covariates. Inverse variance weighting and random-effects modeling was used in all meta-analyses. The presence of significant data heterogeneity, as measured using the I^2 statistic ($I^2 > 50\%$ was considered to represent possible substantial uncertainty, as conveyed in the Cochrane Handbook (Anon., 2011), did not preclude data pooling, but was noted in the discussion of results. In instances where only a single study was identified, intervention results were excluded from meta-analyses and were qualitatively described. Data permitting, subgroup analyses by age were conducted. Risk of publication bias was assessed via funnel plot inspection and Egger regression test.

3. Results

A total of 2660 citations were retrieved from our search of the literature. Following elimination of duplicates, 1671 citations were retained for title and abstract review. Of these, 52 were retained for full review, along with a single study identified through additional searches. Overall, 16 studies met the inclusion criteria for our study and were subject to data extraction. The study selection process is summarized in Fig. 1, while a justification for articles excluded during full review is included in Appendix C.

3.1. Included studies

Of the 16 studies included, 15 (Cheng et al., 2010; Deng et al., 2010; Li et al., 2011; Liu et al., 2011; Toyokawa et al., 2011; Godoy et al., 2012; Kim et al., 2012; Suess et al., 2012; Zhang et al., 2012; Kuster et al., 2013; Remschmidt et al., 2013; Azor-Martinez et al., 2014; Merk et al., 2014; Torner et al., 2015; Zhang et al., 2013) quantitatively described at least one measure of hand hygiene effectiveness, while eight (Cheng et al., 2010; Deng et al., 2010; Toyokawa et al., 2011; Kim et al., 2012; Suess et al., 2012; Zhang et al., 2012; Kuster et al., 2013; Jaeger et al., 2011) measured the effectiveness of facemask use; no studies evaluating the impact of any form of respiratory etiquette, such as covering one's mouth during coughing or sneezing, were identified. All studies derived from the A(H1N1)pdm09 pandemic. Six unique combinations of intervention group and outcome measures were pooled for meta-analysis; two of these had significant data heterogeneity. There were insufficient data to conduct meta-analyses based on age group. The characteristics of individual studies are summarized in Table 2, organized by study and intervention types, while results from individual studies are included in Appendix D.

3.2. Quality assessment

Inter-rater agreement of the quality of included studies was strong. The results of this assessment are included in Tables 3–5, which highlights potential sources of bias across different study types. These are incorporated into the discussion of the implications of findings of our review. Funnel plots assessing the risk of publication bias are included in Fig. 2. Visual inspection of plots was used, as the limited number of included studies and dichotomous nature of the outcome measures of interest make regression testing inappropriate (Deeks et al., 2005).

3.3. Hand hygiene

Fifteen studies were identified from our search that evaluated the effectiveness of some form of hand hygiene in preventing pandemic influenza infection; two were RCTs (Suess et al., 2012; Azor-Martinez et al., 2014), eight were case-control studies (Cheng et al., 2010; Deng et al., 2010; Li et al., 2011; Liu et al., 2011; Godoy et al., 2012; Zhang et al., 2012; Torner et al., 2015; Zhang et al., 2013), three were cohort studies (Kuster et al., 2013; Remschmidt et al., 2013; Merk et al., 2014) and two were cross-sectional surveys (Toyokawa et al., 2011; Kim et al., 2012). Of the studies that could not be pooled for meta-analysis, two RCTs reported a significant effect of hand hygiene. One reported that the incidence and proportion of school absence associated with pandemic influenza decreased in schools where a hand sanitizer intervention was implemented (Azor-Martinez et al., 2014), while the other found that hand hygiene in conjunction with facemask use reduced risk of secondary influenza infection (OR = 0.26; 95% confidence

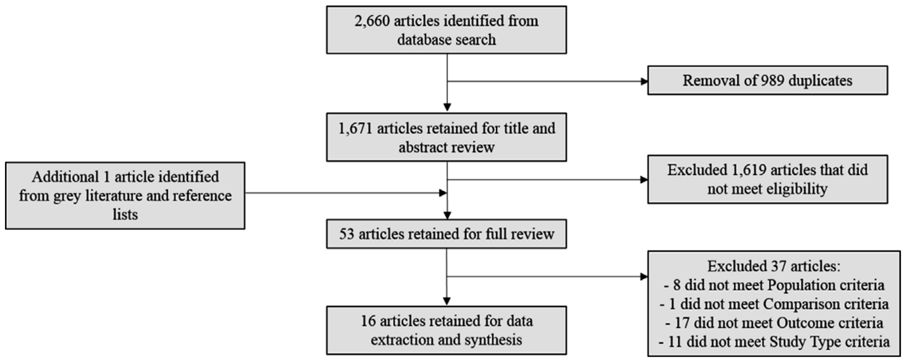

Fig. 1. Data selection process.

Table 2
Summary of included studies.

Study	Type of Study	Population	Participants (N)	Intervention(s)	Outcome(s)
Azor-Martinez et al. (2014)	RCT	Children aged 4–12 in Spain	1,616	Hand sanitizer	School absenteeism
Cheng et al. (2010)	Case-control study	Healthcare workers in Hong Kong	836	Surgical mask use and hand hygiene	Laboratory-confirmed influenza infection
Deng et al. (2010)	Case-control study	Healthcare workers in Beijing, China	280	Surgical masks and use of disposable tissues for hand hygiene	Laboratory-confirmed influenza infection
Godoy et al. (2012)	Multicenter case-control study	Inpatients and individuals who received primary care at participating centers	3,087	Hand hygiene	Hospital admission with laboratory-confirmed influenza
Jaeger et al. (2011)	Cohort study	Healthcare workers in Southern California	63	Surgical masks and N95 respirators	Laboratory-confirmed influenza infection
Kim et al. (2012)	Cross-sectional survey	School-aged children in South Korea	15,945	Handwashing and facemask use	Laboratory-confirmed influenza infection
Kuster et al. (2013	Cohort study	Adult healthcare and non-healthcare workers in Toronto, Canada	732	Hand hygiene and facial protection	Laboratory-confirmed influenza infection
Li et al. (2011)	Case-control study	Students 15–21 years old in Guangzhou, China	1,644	Handwashing	Laboratory-confirmed influenza infection
Liu et al. (2011)	Case-control study	Individuals in Beijing, China	216	Handwashing	Secondary household infection (diagnosis)
Merk et al. (2014)	Cohort study	Individuals 17–95 in Stockholm, Sweden	4,365	Handwashing	Influenza-like illness
Remschmidt et al. (2013)	Cohort study	German households with an infected individual ≥2 years old	375	Handwashing	Secondary household infection (ILI)
Suess et al. (2012)	Cluster RCT	Households in Berlin, Germany with an infected individual ≥2 years old	302	Facemasks and hand hygiene	Laboratory-confirmed secondary influenza infection
Torner et al. (2015)	Multicenter case-control study	Outpatient children 6 months to 7 years old in Spain	478	Hand hygiene	Laboratory-confirmed influenza infection
Toyokawa et al. (2011)	Cross-sectional survey	Healthcare workers in Kobe, Japan	269	Hand hygiene, surgical masks, and N95 respirators	Laboratory-confirmed influenza infection
Zhang et al. (2012)	Case-control study	Healthcare workers in Beijing, China	255	Hand hygiene and mask use	Laboratory-confirmed influenza infection
Zhang et al. (2013)	Case-control study	Households in China	162 (households)	Handwashing	Laboratory-confirmed secondary influenza infection

Table 3
Risk of bias assessment of included RCTs.

RCT	Risk of Bias (low, high, unclear)						
	Random Sequence Generation	Allocation Concealment	Performance Bias	Detection Bias	Attrition Bias	Reporting Bias	Other Bias
Azor-Martinez et al. (2014)	Low	Unclear	High	High	Low	Low	High
Suess et al. (2012)	Unclear	Low	Low	Unclear	Low	High	None

interval (CI) 0.07–0.93) (Suess et al., 2012). These were not pooled because they did not have a comparable outcome measure or single intervention, respectively. A single cohort study reported that each 10% increase in healthcare worker adherence to hand hygiene recommendations resulted in a reduced risk of influenza infection (OR = 0.84; 95% CI 0.73–0.98) (Kuster et al., 2013), but was not pooled because it did not provide estimates of effect that compared an intervention to a control. Two cross-sectional surveys reported a non-significant protective effect of subjectively reported “frequent” hand-washing, with OR = 0.99 (95% CI 0.96–1.02) (Kim et al.,

Table 4
Risk of bias assessment of included cohort studies.

Cohort Study	Risk of Bias[a]								
	Exposed Cohort Representa-tiveness	Non-Exposed Cohort Selection	Ascertainment of Exposure	Absence of Outcome at Start	Comparability of Cohorts	Assessment of Outcome	Length of Follow Up	Adequacy of Follow up	Total Score
Jaeger et al. (2011)	0	1	0	0	0	1	1	1	4
Kuster et al. (2013)	1	0	0	1	1	1	1	1	6
Merck et al., (2014)	1	1	0	0	1	0	1	1	5
Remschmidt et al. (2013)	0	1	1	0	0	0	1	0	3

[a] Score of 0 indicates risk of bias; a score of 1 or 2 was awarded if the study took appropriate measures to limit the risk of bias. The forms and criteria used for quality assessment can be found at (Higgins et al., 2011) for RCTs and (Wells et al., 2014) for case-control and cohort studies.

Table 5
Risk of bias assessment of included case-control studies.

Case-Control Study	Risk of Bias[a]								
	Case Definition	Case Represen-tativeness	Selection of Controls	Definition of Controls	Comparability of Cases and Controls	Ascertainment of Exposure	Method of Ascertainment	Non-Response Rate	Total Score
Cheng et al. (2010)	1	1	1	1	0	1	1	1	7
Deng et al. (2010)	1	0	0	1	0	0	1	1	4
Godoy et al. (2011)	1	0	1	1	0	0	1	0	4
Li et al. (2011)	0	1	1	0	0	1	1	1	5
Liu et al. (2011)	0	1	1	1	2	0	1	1	7
Torner et al. (2015)	1	0	1	1	2	0	1	1	7
Zhang et al. (2013)	1	1	1	1	1	0	1	1	7
Zhang et al. (2012)	1	1	1	1	2	0	0	0	6

[a] Score of 0 indicates risk of bias; a score of 1 or 2 was awarded if the study took appropriate measures to limit the risk of bias. The forms and criteria used for quality assessment can be found at (Higgins et al., 2011) for RCTs and (Wells et al., 2014) for case-control and cohort studies.

2012) and OR = 0.58 (95% CI 0.07–5.13) (Toyokawa et al., 2011), but were excluded from meta-analysis due to the innately high bias in cross-sectional surveys.

The remaining studies were pooled to examine five intervention-outcome comparisons, included in Fig. 3. Meta-analysis of five studies (Li et al., 2011; Liu et al., 2011; Godoy et al., 2012; Torner et al., 2015; Zhang et al., 2013) comparing the frequency of hand-washing with laboratory-confirmed influenza found a significant protective effect, but also significant statistical heterogeneity (Fig. 3a; N = 5789; OR = 0.74; 95% CI 0.56–0.97; I^2 = 72%). However, this protective effect was even more pronounced in a subgroup analysis excluding studies where frequency was subjectively defined by the study participants, and retaining those that reported a minimum number of times study participants washed their hands daily (Fig. 3b; N = 3930; OR = 0.62; 95% CI 0.52–0.73; I^2 = 0%) (Godoy et al., 2012; Torner et al., 2015; Zhang et al., 2013).

A separate meta-analysis of two cohort studies (Remschmidt et al., 2013; Merk et al., 2014) comparing hand-washing frequency with self-reported influenza-like illness (ILI) found a non-significant increase in risk associated with hand-washing (Fig. 3c; N = 4740; RR = 1.12; 95% CI 0.76-1.64; I^2 = 0%). A meta-analysis of two case-control studies (Godoy et al., 2012; Torner et al., 2015) examining the subjectively defined "occasional" use of alcohol-based sanitizers also found a non-significant risk increase in the presence of significant statistical heterogeneity (Fig. 3d; N = 3565; OR = 1.04; 95% CI 0.57–1.89; I^2 = 68%).

Hand hygiene motivated by influenza exposure was found to be significantly protective in two cases. Occasional hand hygiene both following contact with an index case (Fig. 3e; N = 1371; OR = 0.29; 95% CI 0.09-0.93; I^2 = 31%) (Cheng et al., 2010; Deng et al., 2010; Zhang et al., 2012) and following contact with contaminated surfaces (Fig. 3f; N = 3565; OR = 0.65; 95% CI 0.50–0.83; I^2 = 0%) (Godoy et al., 2012; Torner et al., 2015) was found to protect against confirmed pandemic influenza infection.

3.4. Facemask use

Eight studies evaluated the effectiveness of facemask use in preventing pandemic influenza infection (Cheng et al., 2010; Deng et al., 2010; Toyokawa et al., 2011; Kim et al., 2012; Suess et al., 2012; Zhang et al., 2012; Kuster et al., 2013; Jaeger et al., 2011). One cohort study reported that the risk of influenza infection among healthcare workers decreases for each 10% increase in adherence to facial protection guidelines (OR = 0.92; 95% CI 0.79–1.07) (Kuster et al., 2013) was not pooled for meta-analysis because it did not provide estimates of effect comparing an intervention to a control. A cluster randomized control trial found a significantly protective effect of facemask use (OR = 0.28; 95% CI 0.08–0.98) (Suess et al., 2012). A cohort study found a non-significant protective effect (RR = 0.09; 0.00–1.60)(Jaeger et al., 2011) One cross-sectional survey reported a significant protective effect of continuous mask use in children, relative to non-users (OR = 0.51; 95% CI 0.30-0.88), but a non-significant risk increase in irregular users relative to non-users (OR = 1.02; 95% CI 0.83–1.25) (Kim et al., 2012). Another cross-sectional survey reported a non-significant risk increase associated with frequent use of surgical masks (OR = 6.59; 95% CI 0.55–78.3) and N95 respirators (OR = 2.28; 95% CI 0.20–20.2) relative to infrequent use, but is based on a small sample size (N = 87) (Toyokawa et al., 2011). Of the remaining three studies pooled for meta-analysis (Cheng et al., 2010; Deng et al., 2010; Suess et al., 2012; Zhang et al., 2012; Jaeger et al., 2011), all reported on the use of facemasks among healthcare workers dealing with infected patients. Meta-analysis found a non-significant protective effect of mask use in preventing influenza infection (Fig. 3g; N = 1371; OR = 0.53; 95% CI 0.16–1.71; I^2 = 48%). If the randomized control trial and cohort study were pooled with the case–control studies, heterogeneity decreased and a significant protective effect was found (not illustrated: N = 1736; OR = 0.41 95% CI 0.18–0.92; I^2 = 35%).

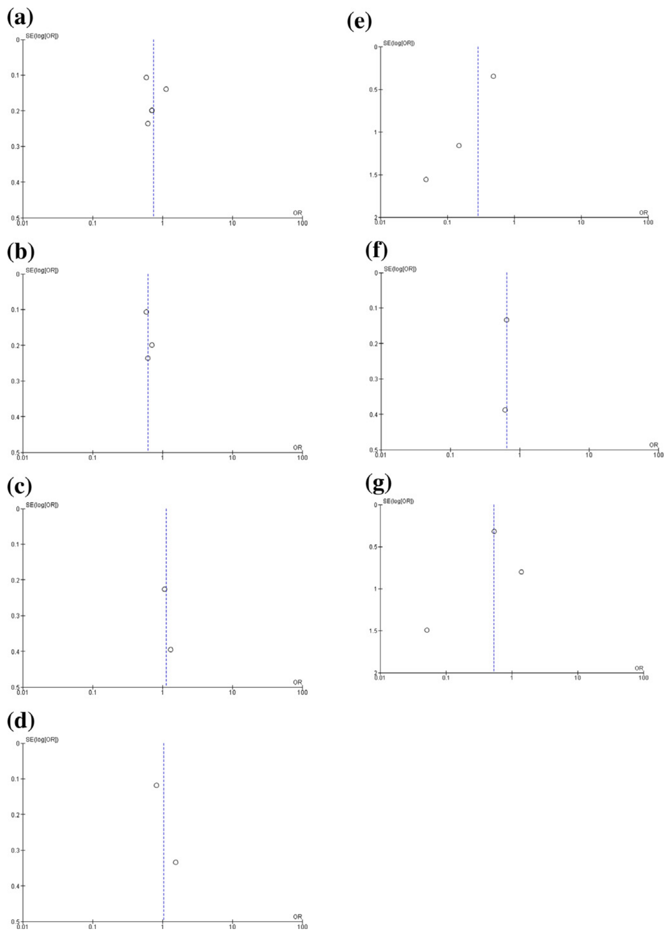

Fig. 2. Funnel plots assessing publication bias in meta-analysis results for (a) hand-washing frequency and influenza; (b) subgroup analysis of hand-washing frequency and influenza; (c) hand-washing frequency and ILI; (d) hand sanitizer use and influenza; (e) hand hygiene after contact with an index case and influenza; (f) hand hygiene after contact with contaminated surfaces and influenza; and (g) facemask use and influenza.

4. Discussion

Analyses of hand hygiene found significant protective effects associated with frequent hand-washing and hand-washing after contact with an index patient or a contaminated surface. These results compare favourably to the results of a systematic review of RCTs evaluating hand hygiene effectiveness during seasonal influenza epidemics, which found a significant protective effect associated with a combination of hand hygiene and facemask use, but no significant effect of hand hygiene alone in preventing influenza infection (Wong et al., 2014). Non-significant increases in risk were associated with hand-washing frequency and ILI and with the occasional use of hand sanitizer and influenza, although these results are based on small samples size and subjective definitions of intervention and outcome measures by primary study authors.

No studies were found that evaluated the effectiveness of respiratory etiquette. However, a recent study evaluated the effectiveness of cough etiquette maneuvers in blocking aerosol particles, finding that they did not block the release or dispersion of aerosol droplets, particularly those smaller than one micron in size (Zayas et al., 2013). As a virus, influenza particles are extremely small, measuring 0.08–0.12 μm in diameter (Stanley, 1944), and could easily be carried in small droplets expelled during coughing or sneezing.

The present systematic review is the first to successfully quantify the effectiveness of PPMs in preventing pandemic influenza infection. Several past reviews have attempted to produce an estimate of effect by reviewing the impact of personal protective measures on transmission of multiple respiratory viruses (Aledort et al., 2007; Bin-Reza et al., 2012; Jefferson et al., 2010; Jefferson et al., 2011). Jefferson and colleagues, for example, pooled case-control study data to calculate estimates of effect of handwashing eleven times a day and simple mask-wearing against SARS transmission, estimating OR of 0.54 (95% CI 0.44–0.67) and 0.32 (95% CI 0.26–0.39), respectively; these do not differ significantly from our own estimates. However, as the authors of one of these reviews recognized, observational studies of SARS are "of limited use for guiding policy on influenza" (Bin-Reza et al., 2012). This is because the epidemiology of SARS differs substantially from that of influenza: SARS transmission tends to occur predominantly in nosocomial settings and infection rarely affects children, involves a long incubation period and low infectiousness in the early stages (Bin-Reza et al., 2012). It should also be noted that, across the reviews mentioned above, the latest search conducted was in January, 2011; all but one of our included studies were published after this date, demonstrating that primary research associated with the A(H1N1)pdm09 strain was still being published at the time these reviews were conducted.

It has been postulated that the effectiveness of PPMs during seasonal influenza epidemics may differ during an influenza pandemic (Bell et al., 2006; Aiello et al., 2010b; Canini et al., 2010; Cowling et al., 2009; MacIntyre et al., 2009a), as public anxiety may increase rates of intervention adherence. There is also uncertainty regarding the relative importance of contact, droplet and airborne routes of transmission in driving influenza infection (Weinstein et al., 2003; Mubareka et al., 2009), which will impact the importance of PPMs targeting a particular route (hand hygiene for contact transmission, respiratory etiquette and facemask use for airborne and droplet transmission).

The role of different routes of transmission may shift during influenza pandemics, given their unpredictable seasonality relative to the usual Northern Hemisphere flu season, which tends to run from October through March but peaks between December and February (CDC, 2016). Colder temperatures (≤4 °C) tend to prolong the environmental persistence of influenza A (Poulson et al., 2016), which could increase the relative burden of contact transmission and the importance of hand hygiene after contact with contaminated surfaces.

Conversely, studies using guinea pigs have found that high temperatures (≥30 °C) prevent aerosol transmission of influenza, but do not affect contact transmission (Lowen et al., 2007, 2008). Meanwhile, low relative humidity (20–30%) appears to promote influenza virus survival in air, increasing aerosol and droplet transmission; these are inhibited at high relative humidity (≥80%) (Lowen et al., 2007; Killingley and Nguyen Van-Tam, 2013). Taken together, variability in adherence and transmission patterns may alter the effectiveness of PPMs during an influenza pandemic relative to a seasonal epidemic; this uncertainty has resulted in challenges for health policy and infection control efforts (Killingley and Nguyen Van-Tam, 2013).

Enhancing knowledge in this area is crucial to informing recommendations on the use of individual protective measures during future influenza pandemics. We conducted a systematic review of the primary literature, pooling data where possible and appropriate to arrive at quantitative estimates of intervention effectiveness. The primary finding was that regular hand hygiene was significantly protective in protecting from pandemic influenza infection, while facemask use was not significantly protective

The significant protective effect of hand hygiene following contact with infected individuals or contaminated cases, which were

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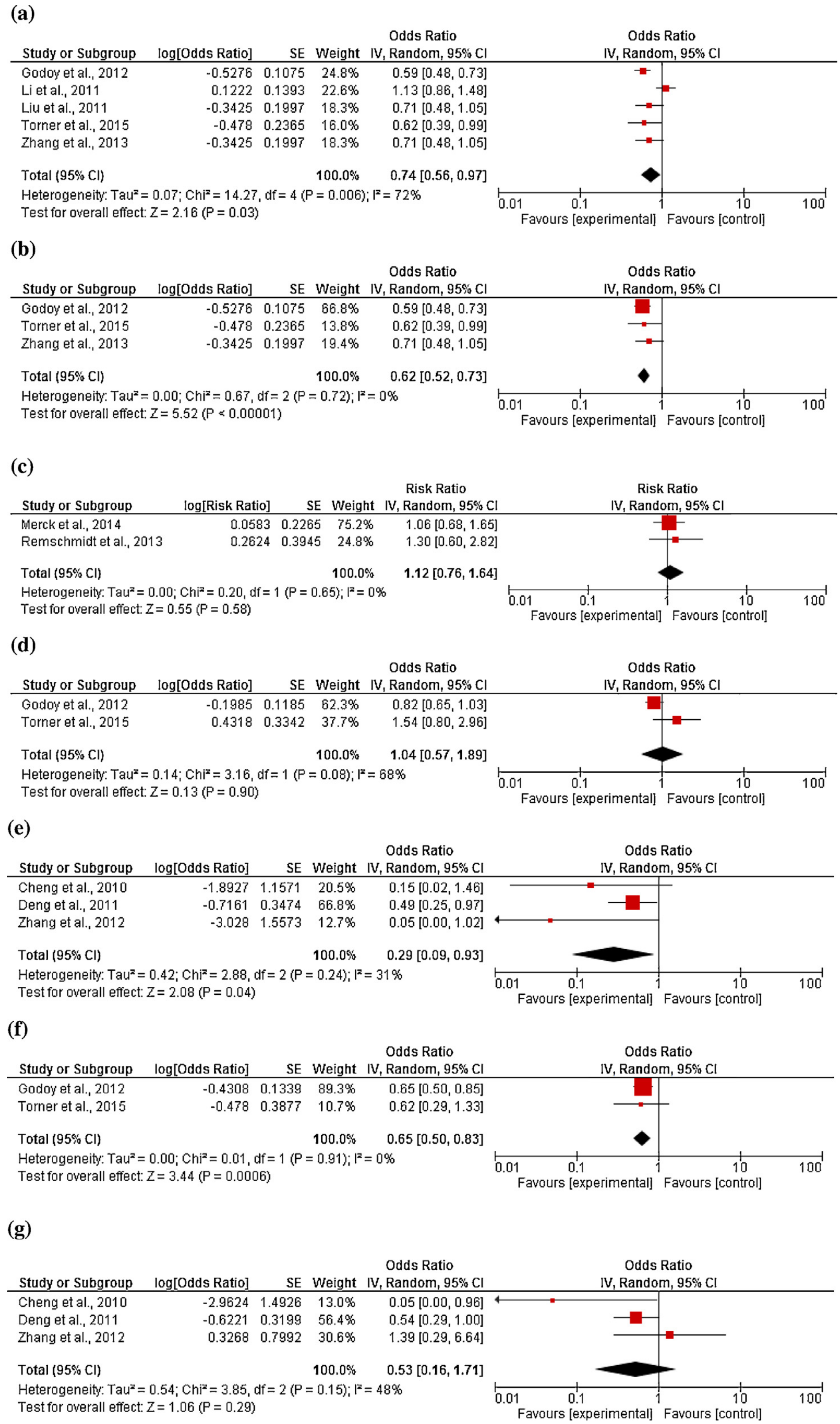

Fig. 3. Forest plots of meta-analysis results of for (a) hand-washing frequency and influenza; (b) subgroup analysis of hand-washing frequency and influenza; (c) hand-washing frequency and ILI; (d) hand sanitizer use and influenza; (e) hand hygiene after contact with an index case and influenza; (f) hand hygiene after contact with contaminated surfaces and influenza; and (g) facemask use and influenza.

found to be comparable to general hand hygiene practices; this supports the position that protective measures both during and immediately following viral exposure will drive intervention effectiveness. While this seems intuitively reasonable, an important implication is that the frequency of performing such maneuvers may need to increase in pandemic situations, where attack rates

and viral loads are likely to be higher than during seasonal epidemics (Jefferson et al., 2014), increasing the frequency of exposure events.

Our systematic review is not without limitations. Out of a recognition that little non-pharmaceutical intervention research that has been conducted in pandemic settings, we took a broad approach to the search strategy, combining multiple intervention-outcome pairs. This did not restrict depth of analysis, however, as data were still limited. Second, most studies included in our review have a moderate-to-high risk of bias, which may limit the interpretability of their results. Inappropriate or unspecified ascertainment of exposure was the most common source of potential bias (Deng et al., 2010; Li et al., 2011; Godoy et al., 2012; Zhang et al., 2012; Kuster et al., 2013; Merk et al., 2014; Torner et al., 2015; Zhang et al., 2013; Jaeger et al., 2011), due to a lack of blinding and reliance of subject self-reporting. While more logistically complicated and resource-intensive, prospective studies that verify subject behaviour would enhance understanding of intervention effectiveness. The representativeness of cases (Deng et al., 2010; Godoy et al., 2012; Torner et al., 2015) and exposed cohorts (Li et al., 2011; Remschmidt et al., 2013; Jaeger et al., 2011), along with their comparability to control groups (Deng et al., 2010; Li et al., 2011; Godoy et al., 2012; Remschmidt et al., 2013; Torner et al., 2015; Jaeger et al., 2011), present other sources of bias, as the potential for selection bias was often present, and studies often failed to account for important confounding factors, such as vaccination status.

The non-blinded, retrospective nature of most studies included in our review presents a risk of performance, detection, and reporting biases, which could over-estimate the true effectiveness of PPMs in preventing influenza infection, as cases and controls may misjudge their adoption of PPMs in order to rationalize their infection status. Given the overall lack of data on this subject, quality-based subgroup analyses were not conducted. A range of economical, logistical and ethical barriers present substantial challenges in the design of controlled, prospective pandemic influenza intervention trials; consequently, it was decided that the potential importance of non-pharmaceutical interventions justifies the decision to acquire as much data as possible, despite risks of biased results. Assessment of funnel plots (Fig. 2) demonstrated some asymmetry and gaps; this may be indicative of publication bias, but is it impossible to conclude with certainty given the small number of studies included in each meta-analysis. It should also be noted that all available data were obtained from studies conducted within the context of the A(H1N1)pdm09 pandemic; this unavoidable constraint may limit the generalizability of our findings to future pandemics of unknown severity. It would be inappropriate to extrapolate this across all strains of past and future pandemics, which may differ in terms of pathogenicity, timing and public response.

Important knowledge gaps persist. It is unclear what constitutes an appropriate “threshold” for adequate, protective hand hygiene and facemask use; it is likely that this will vary depending on individual factors such as exposure, susceptibility and risk of adverse outcomes. This presents challenges in recommending appropriate behaviour during pandemic situations. Study questions using subjective terms to define frequency of PPM use, such as “rarely”, “occasionally” or “sometimes”, contribute to this problem. A study of facemask use (Kim et al., 2012), for example, found a significant protective effect of regular use relative to no use, but not of irregular use relative to no use; it is unclear how much time spent wearing a facemask is necessary to constitute “continuous”. This self-reporting by study subjects of their own intervention status likely contributed to the observed heterogeneity, complicating interpretation of the findings. Studies based on the exact number of times an action was performed daily are likely to provide more reliable results, although such studies are also at risk of recall bias. Small sample sizes have limited the statistical power of our meta-analyses, and the relative merits of use different forms of PPMs are uncertain.

Given the questionable effectiveness of respiratory etiquette, mask use and hand hygiene should form the foundation of protective behavior. As compliance with good hand hygiene practices may be higher than that for facemasks, which have been poorly accepted in the past (MacIntyre et al., 2009b; Tooher et al., 2013), an optimal intervention strategy may combine broad recommendations for frequent hand hygiene, combined with targeted facemask use among high-risk populations (healthcare workers, schools-aged children, the elderly). Risk communication strategies should clarify locations and situations where viral contact is likely, emphasizing the value of engaging in protective behaviours during and immediately following exposure to these environments.

5. Conclusion

This review constitutes a contribution to pandemic influenza research, presenting the first systematic review and meta-analysis to quantify the effectiveness of PPMs in preventing pandemic influenza transmission. While data were not available on the effectiveness of respiratory etiquette, hand hygiene was found to be significantly effective in preventing infection. Facemask use demonstrated mixed results, but a randomized control trial suggests that it is effective. Future studies are needed to evaluate the relative impact of different routes of influenza transmission, and how this may shift between seasonal and pandemic settings. Despite persisting knowledge gaps in relative effectiveness between interventions and across population groups, results suggest that campaigns to increase the frequency of hand hygiene, alongside use of facemasks in situations with a high risk of exposure, are likely to contribute to preventing pandemic influenza infection.

Conflicts of interest

None declared.

Author contributions

PSH conceived the project, developed the search strategy and protocol, conducted article screening, data extraction, and meta-analyses, and drafted the article. JC conducted article screening and data extraction, provided comments and feedback throughout process, and contributed to manuscript writing. LS reviewed the search strategy and contributed to manuscript writing. DK provided comments and feedback throughout process and contributed to manuscript writing.

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Appendix A. PRISMA 2009 checklist for systematic review and meta-analysis of personal protective measure effectiveness (Moher et al., 2009)

Section/topic	#	Checklist item	Reported on page #
Title			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
Abstract			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	1
Introduction			
Rationale	3	Describe the rationale for the review in the context of what is already known.	2
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	2
Methods			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	3
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	4
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	3
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	Appendix B
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	4–5
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	5
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	5
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	5
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	5–6
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I(Humphries, 2013) for each meta-analysis.	5–6
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	5–6
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	6
Results			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	6
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	6–10
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	11–14
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	Appendix D
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	16–19
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	11–14
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression (see Item 16)).	N/A
Discussion			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	19
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	20–21
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	22
Funding			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	N/A

Appendix B. Search strategy for relevant databases

Search conducted June 30, 2016 by Patrick Saunders-Hastings

1. Medline (OVID)

Population
1. Influenza, Human/
2. Exp Influenza A virus A/
3. 1 or 2
4. Pandemics/
5. (pandemic* adj3 (influenza* of flu* or grippe)).tw.
6. 4 or 5
7. 3 and 6

Hand Hygiene:
8. Exp Hand Hygiene/
9. (handwashing or hand washing or hand-washing).tw.
10. ((hand*) adj3 (hygien* or disinfect* or sanitiz* or sanitis* or wash* or scrub* or cleans*)).tw.
11. Or/8-10

Cough/Respiratory Etiquette:
12. Cough/
13. (cough* and (influenza* or flu* or grippe)).tw.
14. ((respirat* or breath* or sneez* or cough*) adj3 (etiquette* or custom* or maneuver* or practic*)).tw.
15. Or/12-14

Masks:
16. Masks/
17. (mask* and (influenza* or flu* or grippe)).tw.
18. (facemask* and (influenza* or flu* or grippe)).tw.
19. (N95* and (influenza* or flu* or grippe)).tw.
20. (N-95* and (influenza* or flu* or grippe)).tw.
21. Or/16-20

Total:
22. 11 or 15 or 21
23. 7 and 22

2. Embase

Population
1. Exp influenza/
2. Exp influenza A virus/
3. 1 or 2
4. Pandemic/
5. (pandemic* adj3 (influenza* or flu* or grippe)).tw.
6. 4 or 5
7. 3 and 6

Hand Hygiene:
8. Exp Hand washing/
9. (handwashing or hand washing or hand-washing).tw.
10. ((hand*) adj3 (hygien* or disinfect* or sanitiz* or sanitis* or wash* or scrub* or cleans*)).tw.
11. Or/8-10

Cough/Respiratory Etiquette:
12. Coughing/
13. (cough* and (influenza* or flu* or grippe)).tw.
14. ((respirat* or breath* or sneez* or cough*) adj3 (etiquette* or custom* or maneuver* or practic*)).tw.
15. Or/12-14

Masks:
16. Exp Mask/
17. (mask* and (influenza* or flu* or grippe).tw.
18. (facemask* and (influenza* or flu* or grippe).tw.
19. (N95* and (influenza* or flu* or grippe).tw.
20. (N-95* and (influenza* or flu* or grippe).tw.
21. Or/16-20

Total:
22. 11 or 15 or 21
23. 7 and 22

3. PubMed

Population

1. Influenza, human [MeSH Terms]
2. Influenzavirus A [MeSH Terms]
3. 1 or 2
4. Pandemic* [MeSH Terms]
5. Pandemic* [Text Word]
6. ((influenza*[Text Word]) or flu* [Text Word]) or grippe [Text Word]
7. 5 and 6
8. 4 or 7
9. 3 and 8

Hand Hygiene:

10. Hand hygiene [MeSH Terms]
11. Hand washing [MeSH Terms]
12. ((handwashing [Text Word]) OR (hand washing [Text Word]) or (hand-washing [Text Word]))
13. (hand* [Text Word])
14. (hygien* [Text Word] or disinfect* [Text Word] or sanitz* [Text Word] or santis* [Text Word] or wash* [Text Word] or scrub* [Text Word] or cleans*[Text Word])
15. 13 and 14
16. 10 or 11 or 12 or 15

Cough Etiquette:

17. Cough*[MeSH Terms]
18. (cough*[Text Word])
19. 6 and 18
20. (respirat* [Text Word] or breath* [Text Word] or sneez* [Text Word] or cough* [Text Word])
21. (etiquette* [Text Word] or custom* [Text Word] or maneuver* [Text Word] or practic* [Text Word])
22. 20 and 21
23. 17 or 19 or 22

Masks:

24. Mask* [MeSH Terms]
25. (mask* [Text Word] or facemask* [Text Word] or N95* [Text Word] or N-95* [Text Word])
26. 6 and 25
27. 24 or 26

Total:

28. 16 or 23 or 27
29. 9 and 28

4. Cochrane Library (Wiley)

Population
1. MeSH descriptor: [Influenza, Human] explode all trees
2. MeSH descriptor: [Influenzavirus A] explode all trees
3. 1 or 2
4. MeSH descriptor: [Pandemics] explode all trees
5. pandemic* (Word variations have been searched)
6. influenza* (Word variations have been searched)
7. flu* (Word variations have been searched)
8. grippe (Word variations have been searched)
9. 6 or 7 or 8
10. 5 and 9
11. 4 or 10
12. 3 and 11

Hand Hygiene:
13. MeSH descriptor: [Hand Hygiene] explode all trees
14. MeSH descriptor: [Hand Disinfection] explode all trees
15. (handwashing or hand washing or hand-washing) (Word variations have been searched)
16. ((hand*) adj3 (hygien* or disinfect* or sanitiz* or sanitis* or wash* or scrub* or cleans*)) (Word variations have been searched)
17. 13 or 14 or 15 or 16

Cough Etiquette:
18. MeSH descriptor: [Cough] explode all trees
19. ((cough*) and (influenza* or flu* or grippe)) (Word variations have been searched)
20. ((respirat* or breath* or sneez* or cough*) adj3 (etiquette* or custom* or maneuver* or practic*)) (Word variations have been searched)
21. Or/18-20

Masks:
22. MeSH descriptor: [Masks] explode all trees
23. (mask* or facemask* or N95* or N-95*) (Word variations have been searched)
24. (influenza* or flu* or grippe) (Word variations have been searched)
25. 23 and 24
26. 22 or 25

Total:
27. 17 or 21 or 26
28. 12 and 27

5. CINAHL

Population
1. (MH “Influenza+”)
2. (MH “Pandemic+”)
3. TX pandemic*
4. TX (influenza* or flu* or grippe)
5. 3 and 4
6. 2 or 5
7. 1 and 6

Hand Hygiene:
8. (MH hand hygiene)
9. (MH hand washing)
10. (MH hand disinfection)
11. TX (handwashing or hand washing or hand-washing)
12. (TX hand*)
13. TX (hygien* or disinfect* or sanitiz* or sanitis* or wash* or scrub* or cleans*)
14. 12 and 13
15. 8 or 9 or 10 or 11 or 14

Cough Etiquette:
16. (MH cough*)
17. TX cough*
18. 4 and 17
19. TX (respirat* or breath* or sneez* or cough*)
20. TX (etiquette* or custom* or maneuver* or practic*)
21. 19 and 20
22. 16 or 18 or 21

Masks:
23. (MH Mask*)
24. TX (mask* or facemask* or N95* or N-95*)
25. 4 and 24
26. 23 or 25

Total:
27. 15 or 22 or 26
28. 7 and 27

Appendix C. Articles excluded during full review

Reference	Reason for exclusion (exclusion category: description)
Agolory, S.G.; Barbot, O.; Averhoff, F.; Weiss, D.; Wilson, E.; Egger, J.; Miller, J.; Ogbuanu, I.; Walton, S.; Kahn, E. Implementation of non-pharmaceutical interventions by new york city public schools to prevent 2009 influenza a. *PloS one* **2013**, *8*, e50916.	Outcome: Study does not evaluate influenza transmission.
Alexander, D.C.; Winter, A.L.; Eshaghi, A.; Dooling, K.; Frenette, C.; De Villa, E.; Varia, M.; Marchand-Austin, A.; Jamieson, F.; Gubbay, J.B. Transmission of influenza a pandemic (h1n1) 2009 virus in a long-term care facility in ontario, canada. *Infection control and hospital epidemiology* **2010**, *31*, 1300–1302.	Outcome: Risk of pandemic influenza infection not examined.
Ang. B.; Poh, B.F.; Win, M.K.; Chow, A. Surgical masks for protection of health care personnel against pandemic novel swine-origin influenza a (h1n1)-2009: Results from an observational study. *Clinical Infectious Diseases* **2010**, *50*, 1011–1014.	Outcome: Risk of pandemic influenza infection not examined.
Becker, C. Influenza pandemic – not all face masks are equally protective. *Pharmazeutische Zeitung* **2006**, *151*, 38–40.	Study type: Commentary
Brantsaeter, A.B. [did vaccines and hygiene recommendations affect the pandemic?]. *Pavirket vaksine og hygienerad pandemien?* **2011**, *131*, 662.	Study type: Commentary
Canini, L.; Andreoletti, L.; Ferrari, P.; Angelo, R.D.; Blanchon, T.; Lemaitre, M.; Filleul, L.; Ferry, J.P.; Desmaizieres, M.; Smadja, S., *et al.* Surgical mask to prevent influenza transmission in households: A cluster randomized trial. *PloS one* **2010**, *5*, e13998.	Population: Population not exposed to pandemic influenza.
Cauteren, D.V.; Vaux, S.; Valk, H.d.; Strat, Y.L.; Vaillant, V.; Levy-Bruhl, D. Burden of influenza, healthcare seeking behaviour and hygiene measures during the a(h1n1)2009 pandemic in france: A population based study. *BMC public health* **2012**, *12*, 947.	Outcome: Study does not examine risk of pandemic influenza transmission.
Cohen, N.J.; Callahan, D.B.; Gonzalez, V.; Balaban, V.; Wang, R.T.; Pordell, P.; Beato, R.; Oyervides, O.; Huang, W.T.; Massoudi, M.S. Respiratory illness in households of school-dismissed students during pandemic (h1n1) 2009. *Emerg Infect Dis* **2011**, *17*, 1756–1757.	Study type: Letter to the editor
Cowling, B.J.; Chan, K.H.; Fang, V.J.; Cheng, C.K.; Fung, R.O.; Wai, W.; Sin, J.; Seto, W.H.; Yung, R.; Chu, D.W., *et al.* Facemasks and hand hygiene to prevent influenza transmission in households: A cluster randomized trial. *Annals of internal medicine* **2009**, *151*, 437–446.	Population: Not pandemic influenza
Cowling, B.J.; Leung, G.M. Simple physical interventions such as hand washing and wearing masks can reduce spread of respiratory viruses. *Evidence-Based Medicine* **2010**, *15*, 3.	Study type: Commentary
Dawes, M. Using physical barriers to reduce the spread of respiratory viruses. *BMJ* **2008**, *336*, 55–56.	Study type: Commentary
Delabre, R.M.; Lapidus, N.; Salez, N.; Mansiaux, Y.; de Lamballerie, X.; Carrat, F. Risk factors of pandemic influenza a/h1n1 in a prospective household cohort in the general population: Results from the copanflu-france cohort. *Influenza and other respiratory viruses* **2015**, *9*, 43–50.	Population: Not pandemic influenza
Deris, Z.Z.; Hasan, H.; Sulaiman, S.A.; Wahab, M.S.; Naing, N.N.; Othman, N.H. The prevalence of acute respiratory symptoms and role of protective measures among malaysian hajj pilgrims. *J Travel Med* **2010**, *17*, 82–88.	Population: Not pandemic influenza
Dominguez, A.; Alonso, J.; Astray, J.; Baricot, M.; Canton, R.; Castilla, J.; Castro, A.; Delgado, M.; Godoy, P.; Gonzalez-Candelas, F., *et al.* Risk factors of influenza (h1n1) 2009 hospitalization and effectiveness of pharmaceutical and nonpharmaceutical interventions in its prevention. A case-control study. *Revista espanola de salud publica* **2011**, *85*, 3–17.	Outcome: Study does not report quantified impact of interventions on pandemic influenza infection
Dos Santos, R.P.; Konkewicz, L.R.; Nagel, F.; Lisboa, T.; Jacoby, T.; Gastal, S.L.; Kuplich, N.M.; Sander, G.; Pires, M.; Lovatto, C.G. The 2009 h1n1 influenza a pandemic and hand hygiene practices in a hospital in the south of brazil. *Infection control and hospital epidemiology* **2010**, *31*, 1313–1315.	Outcome: Study does not report quantified impact of interventions on pandemic influenza infection
Dzyakanava, V.; Burningham, K.; Stahl, J. Virucidal efficacy of topical antiseptics versus a novel strain of influenza h1n1. *International Journal of Infectious Diseases* **2010**, *14*, e248.	Outcome: Study does not examine risk of pandemic influenza infection
Elachola, H.; Assiri, A.M.; Memish, Z.A. Mass gathering-related mask use during 2009 pandemic influenza a (h1n1) and middle east respiratory syndrome coronavirus. *International journal of infectious diseases: IJID: official publication of the International Society for Infectious Diseases* **2014**, *20*, 77–78.	Study type: Letter to the editor
Flisser, A.; Cruz-Licea, V.; Gonzalez-Dominguez, F. Preventive measures associated with probable cases of a (h1n1) influenza in inhabitants of the federal district of mexico city. *American Journal of Tropical Medicine and Hygiene* **2010**, *83*, 356–357.	Outcome: Study does not report quantified impact of interventions on pandemic influenza infection
Gerald, L.B.; Gerald, J.K.; Zhang, B.; McClure, L.A.; Bailey, W.C.; Harrington, K.F. Can a school-based hand hygiene program reduce asthma exacerbations among elementary school children? *The Journal of allergy and clinical immunology* **2012**, *130*, 1317–1324.	Outcome: Examining asthma exacerbations, not pandemic influenza transmission.
Grayson, M.L.; Melvani, S.; Druce, J.; Barr, I.G.; Ballard, S.A.; Johnson, P.D.; Mastorakos, T.; Birch, C. Efficacy of soap and water and alcohol-based hand-rub preparations against live h1n1 influenza virus on the hands of human volunteers. *Clinical infectious diseases: an official publication of the Infectious Diseases Society of America* **2009**, *48*, 285–291.	Population: Study sheds light on risk of transmission; however, does not explicitly examine transmission of a pandemic influenza.
Harwood, J.L.; LaVan, J.T.; Brand, G.J.; nd. Two aircraft carriers' perspectives: A comparative of control measures in shipboard h1n1 outbreaks. *Disaster Med Public Health Prep* **2012**, *7*, 29–35.	Comparison: there is no comparison group
Hobday, R.A.; Cason, J.W. The open-air treatment of pandemic influenza. *American journal of public health* **2009**, *99 Suppl 2*, S236-242.	Study type: Review article
Lapidus, N.; de Lamballerie, X.; Salez, N.; Setbon, M.; Delabre, R.M.; Ferrari, P.; Moyen, N.; Gougeon, M.-L.; Vely, F.; Leruez-Ville, M., et al. Factors associated with post-seasonal serological titer and risk factors for infection with the pandemic a/h1n1 virus in the French general population. PloS one 2013, 8, e60127.	Outcome: Study does not report quantified impact of interventions on pandemic influenza infection
Larson, E.L.; Cohen, B.; Baxter, K.A. Analysis of alcohol-based hand sanitizer delivery systems: Efficacy of foam, gel, and wipes against influenza a (h1n1) virus on hands. *American Journal of Infection Control* **2012**, *40*, 806–809 804p.	Outcome: Study does not report quantified impact of interventions on pandemic influenza infection
Liu, Y.X.; Suo, J.J.; Du, M.M.; Gao, Z.Y.; Yi, J.M.; Xing, Y.B.; Liu, G.; Zhang, S.B.; Liu, L.; Yao, W., *et al.* Assessment of the risk of nosocomial 2009 h1n1 influenza infection among obstetric care workers. *International Journal of Gynecology and Obstetrics* **2011**, *112*, 140–141.	Study type: case series
Loeb, M.; Dafoe, N.; Mahony, J.; John, M.; Sarabia, A.; Glavin, V.; Webby, R.; Smieja, M.; Earn, D.J.; Chong, S., *et al.* Surgical mask vs n95 respirator for preventing influenza among health care workers: A randomized trial. *Jama* **2009**, *302*, 1865–1871.	Population: Not exposed to pandemic influenza
Loustalot, F.; Silk, B.J.; Gaither, A.; Shim, T.; Lamias, M.; Dawood, F.; Morgan, O.W.; Fishbein, D.; Guerra, S.; Verani, J.R., *et al.* Household transmission of 2009 pandemic influenza a (h1n1) and nonpharmaceutical interventions among households of high school students in san antonio, texas. *Clinical Infectious Diseases* **2011**, *52*, S146-S153.	Outcome: Study does not report quantified impact of interventions on pandemic influenza infection

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Mielke, M.; Nassauer, A. [pandemic influenza: Nonpharmaceutical protective measures in ambulatory care]. *Grippeverdacht in der Hausarztpraxis. So schutzen Sie Ihr Team und andere Patienten.* **2009**, *151*, 32–34.	Study type: Guidance document/commentary
Miller, J.R.; Short, V.L.; Wu, H.M.; Waller, K.; Mead, P.; Kahn, E.; Bahn, B.A.; Dale, J.W.; Nasrullah, M.; Walton, S.E., *et al.* Use of nonpharmaceutical interventions to reduce transmission of 2009 pandemic influenza a (ph1n1) in pennsylvania public schools. *The Journal of school health* **2013**, *83*, 281–289.	Outcome: Study does not report quantified impact of interventions on pandemic influenza infection
Mitka, M. Face masks, respirators might help during pandemic flu outbreak. *Jama* **2007**, *297*, 2338.	Study type: Editorial/commentary
Savolainen-Kopra, C.; Haapakoski, J.; Peltola, P.A.; Ziegler, T.; Korpela, T.; Anttila, P.; Amiryousefi, A.; Huovinen, P.; Huvinen, M.; Noronen, H., *et al.* Hand washing with soap and water together with behavioural recommendations prevents infections in common work environment: An open cluster-randomized trial. *Trials* **2012**, *13*, no pagination.	Population: does not specifically address pandemic influenza infection rates
Simmerman, J.M.; Suntarattiwong, P.; Levy, J.; Gibbons, R.V.; Cruz, C.; Shaman, J.; Jarman, R.G.; Chotpitayasunondh, T. Influenza virus contamination of common household surfaces during the 2009 influenza a (h1n1) pandemic in bangkok, thailand: Implications for contact transmission. *Clinical infectious diseases: an official publication of the Infectious Diseases Society of America* **2010**, *51*, 1053–1061.	Outcome: Study does not report quantified impact of interventions on pandemic influenza infection
Suess, T.; Remschmidt, C.; Schink, S.; Luchtenberg, M.; Haas, W.; Krause, G.; Buchholz, U. Facemasks and intensified hand hygiene in a german household trial during the 2009/2010 influenza a(h1n1) pandemic: Adherence and tolerability in children and adults. *Epidemiol Infect* **2011**, *139*, 1895–1901.	Outcome: Study does not examine risk of pandemic influenza transmission.
Tang, J.W.; Li, Y. Transmission of influenza a in human beings. *Lancet Infectious Diseases* **2007**, *7*, 758.	Study type: Commentary
Weedon, K.M.; Rupp, A.H.; Heffron, A.C.; Kelly, S.F.; Zheng, X.; Shulman, S.T.; Gutman, P.; Wang, D.; Zhou, Y.; Noskin, G.A., *et al.* The impact of infection control upon hospital-acquired influenza and respiratory syncytial virus. *Scandinavian journal of infectious diseases* **2013**, *45*, 297–303.	Population: Compares hand hygiene impact across seasons, not within pandemic period. Given that practices also changed during pandemic season (N95 masks and isolation), these cannot be compared.
Yeom, J.S.; Lee, J.H.; Bae, I.G.; Oh, W.S.; Moon, C.S.; Park, K.H.; Lee, J.H.; Kim, E.S.; Kwak, Y.G.; Lee, C.S. 2009 h1n1 influenza infection in korean healthcare personnel. *European journal of clinical microbiology & infectious diseases: official publication of the European Society of Clinical Microbiology* **2011**, *30*, 1201–1206.	Outcome: Study did not quantify risk of pandemic influenza transmission.
Zakhashvili, K.; Imnadze, P.; Tarkhan-Mouravi, O. Analysis of first cluster outbreak of the pandemic influenza (h1n1) in georgia. *International Journal of Infectious Diseases* **2010**, *14*, e90-e91.	Outcome: Study did not quantify risk of pandemic influenza transmission.

Appendix D. Summary of individual study results

RCT Studies	Population Size	Intervention(s)	Outcome(s)	Risk (Control Group)	Risk (intervention group)	Estimate of Effect (95% CI)
Azor-Martinez et al. (2014)	1616	Hand sanitizer	% total absent days (95% CI)	1 (0.9–1.1)	0.38 (0.32–0.45)	RR: 2.64 (2.16–3.21)
Azor-Martinez et al. (2014)	1616	Hand sanitizer	Incidence of episodes/100 children/day (95% CI)	0.28 (0.22–0.33)	0.11 (0.08–0.15)	RR: 2.50 (1.73–3.62)
Suess et al. (2012)	302	Facemasks	Laboratory-confirmed secondary influenza infection	13/56 (232.1/1000)	6/58 (103.4/1000)	OR: 0.28 (0.08–0.97)
Suess et al. (2012)	302	Facemasks and hand hygiene	Laboratory-confirmed secondary influenza infection	13/56 (232.1/1000)	4/50 (80/1000)	OR: 0.26 (0.07–0.93)

Cohort Studies	Population Size	Intervention(s)	Outcome(s)	Risk (Control Group)	Risk (Intervention Group)	Estimate of Effect (95% CI)
Jaeger et al. (2011)	63	Mask or N95 respirator use	Healthcare-associated, laboratory-confirmed influenza infection	9/43 (209.3/1000)	0/20 (0/1000)	P = 0.047
Kuster et al. (2013)	563	Hand hygiene	Laboratory-confirmed influenza infection	Not reported	Not reported	Adherence to hand hygiene recommendations per 10% increase: OR: 0.84 (0.73–0.98)/AOR: 0.86 (0.74–0.99)
Kuster et al. (2013)	563	Facial protection	Laboratory-confirmed influenza infection	Not reported	Not reported	Adherence to facial protection recommendations per 10% increase: OR: 0.92 (0.79–1.07)/AOR: N/A
Merck et al. (2014)	2865	Handwashing frequency (≥20 vs 2–4 times daily)	Self-reported influenza-like illness	Not reported	Not reported	CRR: 1.23 (0.82–1.85); ARR: 1.06 (0.68–1.67)
Remschmidt et al. (2013)	230	Always/often cleaned hands in general	Self-reported ILI secondary household infection	10/116 (86.2/1000)	16/144 (111.1/1000)	OR: 1.30 (0.6–3.0)
Remschmidt et al. (2013)	48	Always/mostly cleaned hands after physical contact with index patient	Self-reported ILI secondary household infection	2/19 (105.3/1000)	1/29 (34.5/1000)	OR: 0.30 (0.02–3.60)
Remschmidt et al. (2013)	256	Always/mostly cleaned hands after contact with physical items used by the index patient	Self-reported ILI secondary household infection	21/202 (104.0/1000)	5/54 (92.6/1000)	OR: 0.90 (0.30–2.40)

Case-Control Studies	Population Size	Cases	Controls	Interventions	Risk (Control Group)	Risk (Intervention Group)	Estimate of Effect (95% CI)
Cheng et al. (2010)	836	Exposed healthcare workers who became infected with influenza	Exposed healthcare workers who did not become infected with influenza	Exposed person wore surgical mask use during contact with index case	4/268 (14.9/1000)	0/568 (0/1000)	p = 0.01
Cheng et al. (2010)	836	Exposed healthcare workers who became infected with influenza	Exposed healthcare workers who did not become infected with influenza	Index case wore mask during contact with the exposed	4/304 (13.2/1000)	0/532 (0/1000)	p = 0.017
Cheng et al. (2010)	836	Exposed healthcare workers who became infected with influenza	Exposed healthcare workers who did not become infected with influenza	Exposed person practiced hand hygiene after contact with index case	3/262 (11.5/1000)	1/574 (1.74/1000)	p = 0.094
Deng et al. (2011)	280	Exposed healthcare workers who became infected with influenza	Exposed healthcare workers who did not become infected with influenza	Exposed person used disposable tissues to wash hands	41/172 (238.4/1000)	13/98 (132/1000)	OR: 0.49 (0.25–0.97)
Deng et al. (2011)	280	Exposed healthcare workers who became infected with influenza	Exposed healthcare workers who did not become infected with influenza	Exposed person used a surgical mask	21/76 (276.3/1000)	33/194 (170.1/1000)	OR: 0.54 (0.29–1.01)
Godoy et al. (2012)	3087	Individuals hospitalizaed with laboratory-confirmed influenza	Two patients with unplanned hospitalization not due to influenza and one outpatient control not related to influenza	Frequency of handwashing (5–10 times daily vs 1–4 times daily baseline)	320/1056 (303.0/1000)	285/1156 (247.4/1000)	COR: 0.73 (0.60–0.89); AOR 0.65 (0.52–0.84)
Godoy et al. (2012)	3087	Individuals hospitalizaed with laboratory-confirmed influenza	Two patients with unplanned hospitalization not due to influenza and one outpatient control not related to influenza	Frequency of handwashing (> 10 times daily vs 1–4 times daily baseline)	320/1056 (303.0/1000)	181/825 (219.4/1000)	COR: 0.58 (0.46–0.73) AOR: 0.59 (0.44–0.79)
Godoy et al. (2012)	3087	Individuals hospitalizaed with laboratory-confirmed influenza	Two patients with unplanned hospitalization not due to influenza and one outpatient control not related to influenza	Use of alcohol-based sanitizers (sometimes vs never)	533/2069 (267.3/1000)	231/973 (237.4/1000)	COR: 0.83 (0.68–1.01); AOR: 0.82 (0.65–1.02)
Godoy et al. (2012)	3087	Individuals hospitalizaed with laboratory-confirmed influenza	Two patients with unplanned hospitalization not due to influenza and one outpatient control not related to influenza	Handwashing after touching contaminated surfaces (occasionally/always vs never)	196/599 (327.2/1000)	600/2452 (244.7/1000)	COR: 0.58 (0.46–0.73); AOR: 0.65 (0.50–0.84)
Li et al. (2011)	1644	Handwashing ("frequent"/"infrequent")	Laboratory-confirmed influenza infection	88/293 (300.3/1000)	417/1277 (326.6/1000)	OR: 1.13 (0.86–1.49)	
Liu et al. (2011)	216	Individuals who developed secondary infection from infected household member	Individuals who did not develop secondary infection from infected household member	Have the habit of washing hands (yes/no)	Not reported	Not reported	OR: 0.71 (0.48–0.94)
Torner et al. (2015)	478	Child outpatients with confirmed influenza infection	Child outpatients with illness unrelated to influenza or acute respiratory tract infection	Handwashing frequency ($\geq$5 vs 1–4 times daily)	123/230 (534.8/1000)	112/239 (468.6/1000)	COR: 0.69 (0.45–1.04); AOR: 0.62 (0.39–0.99)
Torner et al. (2015)	478	Child outpatients with confirmed influenza infection	Child outpatients with illness unrelated to influenza or acute respiratory tract infection	Use of alcohol-based sanitizers (sometimes vs never)	158/328 (481.7/1000)	77/142 (542.3/1000)	COR: 1.36 (0.85–2.17); AOR: 1.54 (0.80–2.66)
Torner et al. (2015)	478	Child outpatients with confirmed influenza infection	Child outpatients with illness unrelated to influenza or acute respiratory tract infection	Handwashing after touching contaminated surfaces (sometimes vs never)	50/93 (537.6/1000)	184/376 (489.4/1000)	COR: 0.73 (0.41–1.32); AOR: 0.62 (0.29–1.31)
Zhang et al. (2013)	262 households	Household with quarantined individual with influenza infection that experienced a secondary infection	Household with quarantined individual with influenza infection that did not experience a secondary infection	Handwashing frequency ($\geq$3 times daily)	Not reported	Not reported	OR: 0.71 (0.48–0.94)

Zhang et al. (2012)	164	Full-time, exposed healthcare worker infected with confirmed pandemic influenza	Full-time, exposed healthcare worker that did not experience ILI or influenza	Mask-wearing (always vs seldom/never)	2/12 (166.7/1000)	33/152 (217.1/1000)	P = 0.344
Zhang et al. (2012)	255	Full-time, exposed healthcare worker infected with confirmed pandemic influenza	Full-time, exposed healthcare worker that did not experience ILI or influenza	Number of masks used daily (≥2)	18/84 (214.3/1000)	33/171 (193.0/1000)	P = 0.798
Zhang et al. (2012)	28	Full-time, exposed healthcare worker infected with confirmed pandemic influenza	Full-time, exposed healthcare worker that did not experience ILI or influenza	Use of N95 respiratory (vs never wore mask)	2/12 (166.7/1000)	3/16 (187.5/1000)	P = 0.796
Zhang et al. (2012)	255	Full-time, exposed healthcare worker infected with confirmed pandemic influenza	Full-time, exposed healthcare worker that did not experience ILI or influenza	Hand-washing after caring for patient	2/2 (1000/1000)	49/253 (193.7/1000)	N/A
Zhang et al. (2012)	255	Full-time, exposed healthcare worker infected with confirmed pandemic influenza	Full-time, exposed healthcare worker that did not experience ILI or influenza	Hand drying (disposable paper towel vs work clothes/reusable towel	24/95 (252.6/1000)	11/86 (127.9/1000)	P = 0.065

Cross-Sectional Studies	Population Size	Comparison	Interventions	Risk (Control Group)	Risk (Intervention Group)	Estimate of Effect (95% CI)
Kim et al. (2012)	15,945	Children with/without H1N1 infection	Handwashing (frequent/infrequent)	Not reported	Not reported	OR: 0.99 (0.96–1.02)
Kim et al. (2012)	15,945	Children with/without H1N1 infection	Facemasks (continuous vs non-users)	239/4403 (54.3/1000)	14/480 (29.2/1000)	OR: 0.51 (0.30–0.88)
Kim et al. (2012)	15,945	Children with/without H1N1 infection	Facemasks (irregular vs non-users)	239/4403 (54.3/1000)	164/2983 (55.0/1000)	OR: 1.02 (0.83–1.25)
Toyokawa et al. (2011)	97	Healthcare workers with/without H1N1 infection	Hand hygiene (frequent/infrequent)	6/76 (79.0/1000)	1/21 (47.6/1000)	OR: 0.58 (0.07–5.13)
Toyokawa et al. (2011)	87	Healthcare workers with/without H1N1 infection	Surgical masks use in ED (frequent/infrequent)	4/83 (41.2/1000)	1/4 (250/1000)	OR: 6.59 (0.55–78.3)
Toyokawa et al. (2011)	87	Healthcare workers with/without H1N1 infection	N95 respiratory use in ED (frequent/infrequent)	4/77 (52.0/1000)	1/10 (100/1000)	OR: 2.28 (0.20–20.2)

RR = relative rate; CRR = crude relative rate; ARR = adjusted relative rate; OR = odds ratio; COR = crude odds ratio; AOR = adjusted odds ratio.

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